How does organic structure determine organic reactivity? The effect of *ortho*-dimethyl groups on the nucleophilic substitution and alkene-forming elimination reactions of ring-substituted cumyl derivatives

Tina L. Amyes, Tadeusz Mizerski, and John P. Richard

Abstract: The addition of a pair of *ortho*-methyl groups to ring-substituted cumyl derivatives to give the corresponding 2,6-dimethylcumyl derivatives X-**1**-Y leads to modest (<5-fold) changes in the observed rate constant for reaction in 50:50 (v:v) trifluoroethanol–water (I = 0.50, $NaClO_4$). The reactions of X-**1**-Y proceed by a stepwise mechanism through the liberated 2,6-dimethylcumyl carbocations X-**2** that partition between nucleophilic addition of solvent and deprotonation to give good yields (≥ 67%) of the corresponding 2-(2,6-dimethylaryl)propenes X-**3**. The carbocations X-**2** are also trapped by nucleophilic addition of azide ion to give good yields (≥ 68% at $[N_3^-]$ = 0.50 M) of the corresponding 2,6-dimethylcumyl azides X-**1**-N_3. In the presence of high concentrations of azide ion there are constant limiting yields of the alkenes X-**3,** which shows that X-**2** also undergo significant reactions with azide ion as a Brønsted base. The product rate constant ratios for partitioning of the 2,4,6-trimethylcumyl carbocation Me-**2** between reaction with azide ion as a Lewis and a Brønsted base, k_{az}/k_B, the nucleophilic addition of azide ion and solvent, k_{az}/k_s (M^{-1}), and deprotonation by solvent, k_{az}/k_e (M^{-1}), were combined with $(k_{az} + k_B) = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-limited reaction of azide ion to give absolute rate constants for the reactions of Me-**2**. The data show that the addition of a pair of *ortho*-methyl groups to the 4-methylcumyl carbocation to give the sterically hindered Me-**2** results in a 70-fold decrease in the rate constant for nucleophilic addition of solvent to the benzylic carbon, but a 60-fold *increase* in the rate constant for deprotonation of the carbocation by solvent.

Key words: carbocation, *ortho*-substituent effects, steric effects, solvolysis, elimination.

Résumé : L’addition d’une paire de groupes méthyles en *ortho* de dérivés cumyles substitués sur le cycle donne les dérivés 2,6-diméthylcumules X-**1**-Y; leurs vitesses de réaction dans un mélange 50 : 50 (v : v) de trifluoroéthanol–eau (I = 0,50, $NaClO_4$) sont légèrement augmentées (par un facteur d’environ 5). Les réactions des produits X-**1**-Y se produisent par un mécanisme par étapes, par le biais des carbocations 2,6-diméthylcumyles libérés, X-**2**, qui réagissent en partie par une addition nucléophile du solvant ou par une déprotonation conduisant à des bons rendements (≥ 67%) des 2-(2,6-diméthylaryl)propènes correspondants, X-**3**. Les carbocations X-**2** peuvent aussi être piégés par l’addition nucléophile de l’ion azoture qui fournit de bons rendements (≥ 68%, à des $[N_3^+]$ = 0,50 M) des azotures de 2,6-diméthylcumyle correspondants, X-**1**-N_3. En présence d’une concentration élevée d’ion azoture, on observe la formation des alcènes X-**3** avec des rendements limites constants; ceci démontre que les ions X-**2** subissent aussi des réactions significatives avec l’ion azoture agissant comme base de Brønsted. Dans le but de déterminer les constantes de vitesse absolue des réactions de Me-**2**, on a combiné la constante de vitesse de réaction de l’ion azoture limitée par la diffusion ($(k_{az} + k_B) = 5,0 \times 10^9$ M^{-1} s^{-1}) avec les rapports de constante de vitesse des réactions du carbocation 2,4,6-triméthylcumyle, Me-**2**, avec l’ion azoture comme base de Lewis et comme base de Brønsted, k_{az}/k_B, par addition nucléophile de l’ion azoture et du solvant, k_{az}/k_s (M^{-1}), et par déprotonation par le solvant, k_{az}/k_e (M^{-1}). Les données montrent que l’addition d’une paire de groupes méthyles en *ortho* du carbocation 4-méthylcumyle provoque un empêchement stérique qui engendre une diminution (par un facteur de 70) de la constante de vitesse d’addition nucléophilique du solvant sur le carbone benzylique et une augmentation (par un facteur de 60) de la constante de vitesse de déprotonation du carbocation par le solvant.

Mots clés : carbocation, effets de substituants en *ortho*, effets stériques, solvolyse, élimination.

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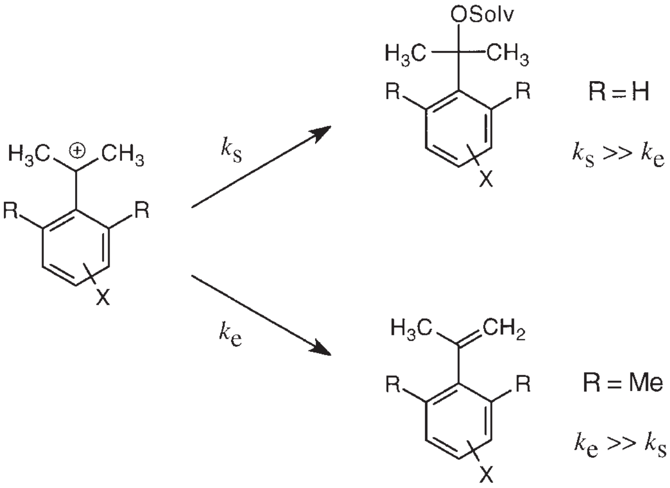
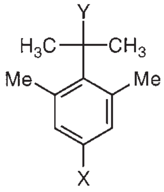
Scheme 1.



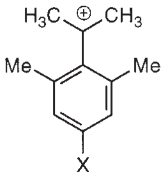
Introduction

We are interested in the effects of changing substrate structure on the stepwise reactions of simple α-methylbenzyl derivatives $XC_6H_4CMe(R)Y$ in nucleophilic solvents. These studies have shown that changes in the α-substituent R result in large changes in the thermodynamic stability of the carbocation intermediates $XC_6H_4CMe(R)^+$ (1, 2), but that the usual fate of these carbocations is their almost exclusive capture at the benzylic carbon by solvent and (or) added nucleophiles. For example, in 50:50 trifluoroethanol–water, liberated ring-substituted cumyl carbocations $XC_6H_4CMe_2^+$, generated from the ionization of cumyl 4-nitrobenzoates or the acid-catalyzed cleavage of cumyl methyl ethers, partition to give >99% of the products of solvolysis and <1% of the α-methylstyrene product of elimination (R = H, $k_s >> k_e$, Scheme 1) (3, 4). This stands in sharp contrast with the report of Creary et al. that in acetic acid or trifluoroethanol, 2,6-dimethylcumyl trifluoroacetate (H-**1**-(trifluoroacetate)) undergoes stepwise reaction through the 2,6-dimethylcumyl carbocation H-**2** to give the alkene H-**3** as the sole product (5). This is a dramatic example of an "*ortho* effect" (6–8), and it suggests that the addition of a pair of *ortho*-methyl groups results in a fundamental change in the partitioning of cumyl carbocations, from the almost exclusive nucleophilic addition of solvent to the benzylic carbon (R = H, $k_s >> k_e$, Scheme 1) to the exclusive loss of a proton to give the corresponding α-methylstyrene (R = Me, $k_e >> k_s$, Scheme 1).

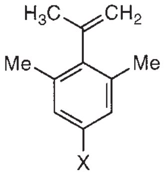
We report here a study of the nucleophilic substitution and elimination reactions of a series of ring-substituted 2,6-dimethylcumyl derivatives X-**1**-Y (X = MeO, Me, H) in 50:50 (v:v) trifluoroethanol–water. The results show that X-**1**-Y undergo stepwise reactions through the liberated carbocations X-**2** that are trapped by the nucleophilic addition of solvent and azide ion to the benzylic carbon. To the best of our knowledge, these reactions represent the first examples of the conversion of a disubstituted sp^2-hybridized carbon attached to a 2,6-disubstituted aryl moiety into a stable tetrahedral adduct. The carbocations X-**2** also undergo proton transfer to solvent and azide and acetate ions to give the alkenes X-**3**. The data provide relative and absolute rate constants for the formation and reaction of the sterically hindered carbocations X-**2** with Brønsted and Lewis bases.



X-**1**-Y



X-**2**



X-**3**

Experimental section

Materials

2-Bromo-*m*-xylene, 2-bromomesitylene, 3,5-dimethylanisole, 4-methoxybenzoyl chloride, 4-nitrobenzoyl chloride, butyllithium, acetone, and 2,2,2-trifluoroethanol were purchased from Aldrich. Sodium azide was purchased from Fluka. 9-Methyl-9-fluorenol was available from a previous study (9). Tetrahydrofuran was distilled from sodium–benzophenone. All other chemicals were reagent grade and were used without further purification. Water for HPLC analysis and kinetic studies was distilled and then passed through a Milli-Q purification system.

Synthesis

^1H NMR spectra were recorded in $CDCl_3$ on Varian spectrometers. Chemical shifts are reported downfield of an internal tetramethylsilane standard at 0 ppm. Melting points were determined using a Mel-Temp apparatus and are uncorrected.

4-Bromo-3,5-dimethylanisole (10), 2-(2,6-dimethylphenyl)-2-propyl alcohol [H-**1**-OH] (5) and 2-(2,4,6-trimethylphenyl)-propene [Me-**3**] (11) were prepared by literature procedures.

2-(2,4,6-Trimethylphenyl)-2-propyl alcohol

Me-**1**-OH was prepared from 2-bromomesitylene by the literature procedure (5) used for the preparation of 2-(2,6-dimethylphenyl)-2-propyl alcohol. Purification by column chromatography on silica gel, eluting with 1:3 ethyl acetate – hexanes, gave the alcohol in 23% yield as a white solid: mp 111–112°C (lit. (12) 111–112°C); ^1H NMR (200 MHz) δ: 6.83 (2H, s, Ar), 2.51 (6H, s, $(CH_3)_2Ar$), 2.23 (3H, s, CH_3Ar), 1.72 (6H, s, $(CH_3)_2$), 1.67 (1H, s, OH).

2-(4-Methoxy-2,6-dimethylphenyl)-2-propyl alcohol

MeO-**1**-OH was prepared from 4-bromo-3,5-dimethylanisole by the literature procedure (5) used for the preparation of 2-(2,6-dimethylphenyl)-2-propyl alcohol. Purification by column chromatography on silica gel, eluting with 1:3 ethyl acetate – hexanes, gave the alcohol in 22% yield as a white solid: mp 96–97°C; ^1H NMR (400 MHz) δ: 6.55 (2H, s, Ar), 3.77 (3H, s, OCH_3), 2.52 (6H, s, $(CH_3)_2Ar$), 1.71 (6H, s, $(CH_3)_2$), 1.66 (1H, s, OH).

2-(2,6-Dimethylphenyl)-2-propyl 4-methoxybenzoate

H-**1**-(4-methoxybenzoate) was prepared by adaptation of a literature procedure (13). Butyllithium (4.4 mL of a 1.6 M solution in hexanes, 7.0 mmol) was added to a solution of 2-(2,6-dimethylphenyl)-2-propyl alcohol (1.06 g, 6.5 mmol) in dry tetrahydrofuran (8 mL) at room temperature under argon and the mixture was stirred for 0.5 h. 4-Methoxybenzoyl chloride (1.2 g, 7.0 mmol) in dry tetrahydrofuran (5 mL) was added and the mixture was heated under reflux for 2 h. The solvent was removed by evaporation and the residue was dissolved in dichloromethane (50 mL), washed with water (50 mL), dried with $MgSO_4$, and evaporated. The resulting yellow crystals were decolorized with activated charcoal and recrystallized twice from hexane to give the ester (0.65 g, 34%) as white crystals: mp 86–87°C; ^1H NMR (200 MHz) δ: 8.00 (2H, d, J = 9 Hz, Ar), 6.98 (3H, m, Ar), 6.92 (2H, d, J = 9 Hz, Ar), 3.87 (3H, s, OCH_3), 2.44 (6H, s, $(CH_3)_2Ar$), 2.00 (6H, s, $(CH_3)_2$).

2-(2,4,6-Trimethylphenyl)-2-propyl 4-methoxybenzoate

Me-**1**-(4-methoxybenzoate) was prepared from 2-(2,4,6-trimethylphenyl)-2-propyl alcohol by the procedure described above for 2-(2,6-dimethylphenyl)-2-propyl 4-methoxybenzoate. Recrystallization from hexane gave the ester in 50% yield: mp 106–107°C; ^1H NMR (200 MHz) δ: 8.00 (2H, d, J = 9 Hz, Ar), 6.92 (2H, d, J = 9 Hz, Ar), 6.80 (2H, s, Ar), 3.87 (3H, s, OCH_3), 2.41 (6H, s, $(CH_3)_2Ar$), 2.21 (3H, s, CH_3Ar), 1.99 (6H, s, $(CH_3)_2$).

2-(4-Methoxy-2,6-dimethylphenyl)-2-propyl 4-methoxybenzoate

MeO-**1**-(4-methoxybenzoate) was prepared from 2-(4-methoxy-2,6-dimethylphenyl)-2-propyl alcohol by the procedure described above for 2-(2,6-dimethylphenyl)-2-propyl 4-methoxybenzoate. Purification by column chromatography on silica gel, eluting with 1:1 ethyl acetate – hexanes, followed by recrystallization from hexane gave the ester in 22% yield as plates: mp 86–87°C; ^1H NMR (400 MHz) δ: 7.99 (2H, d, J = 9 Hz, Ar), 6.91 (2H, d, J = 9 Hz, Ar), 6.52 (2H, s, Ar), 3.86 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 2.43 (6H, s, $(CH_3)_2Ar$), 1.98 (6H, s, $(CH_3)_2$).

2-(2,4,6-Trimethylphenyl)-2-propyl 4-nitrobenzoate

Me-**1**-(4-nitrobenzoate) was prepared from 2-(2,4,6-trimethylphenyl)-2-propyl alcohol and 4-nitrobenzoyl chloride by the procedure described above for 2-(2,6-dimethylphenyl)-2-propyl 4-methoxybenzoate. Recrystallization from ether gave the ester in 18% yield as needles: mp 232–233°C (sl. dec.); ^1H NMR (400 MHz) δ: 8.28 (2H, d, J = 9 Hz, Ar), 8.20 (2H, d, J = 10 Hz, Ar), 6.81 (2H, s, Ar), 2.39 (6H, s, $(CH_3)_2Ar$), 2.22 (3H, s, CH_3Ar), 2.03 (6H, s, $(CH_3)_2$).

2-(4-Methoxy-2,6-dimethylphenyl)propene

MeO-**3** was prepared by dehydration of 2-(4-methoxy-2,6-dimethylphenyl)-2-propyl alcohol by the literature procedure (11) for the preparation of 2-(2,4,6-trimethylphenyl)propene. Purification by distillation gave the alkene in 96% yield: bp 82°C (1 Torr (= 133.3 Pa)); ^1H NMR (400 MHz) δ: 6.60 (2H, s, Ar), 5.27 (1H, broad, CH_2), 4.75 (1H, br, CH_2), 3.78 (3H, s, OCH_3), 2.25 (6H, s, $(CH_3)_2Ar$), 1.94 (3H, s, CH_3).

Product studies

Unless stated otherwise, product studies were carried out in 50:50 (v:v) trifluoroethanol–water at 25°C and I = 0.50 ($NaClO_4$). Reactions were initiated by making a 100-fold dilution of a solution of substrate in acetonitrile into the appropriate reaction mixture and product distributions were determined by HPLC analysis. For reactions at $[N_3^-] \leq 0.05$ M the solutions were buffered with 25 mM cacodylate, 80% anion, which prevented acid-catalyzed breakdown of the solvolysis products. Aqueous solutions containing sodium azide were adjusted to pH ≈ 7 with concentrated $HClO_4$ before use.

The products of the reactions of Me-**1**-(4-methoxybenzoate) ([S] = 2 mM) in the absence of azide ion were analyzed after 2–30 halftimes for reaction of the substrate and were shown to be stable during this time. For reactions in the presence of azide ion the products were analyzed after 30–40 halftimes, because the substrate and the azide ion adduct Me-**1**-N_3 coeluted from the HPLC column. At these long reaction times there was slight (≤5%) breakdown of Me-**1**-N_3 that resulted in significant increases in the relatively small fractional yields of the solvent adducts Me-**1**-OSolv. For the reactions in the presence of 0.05 M azide ion and increasing concentrations of acetate ion the solutions were buffered with acetate, 95% anion. UV spectroscopy showed that under these conditions more than 97% of the azide is in the anionic form. In all cases the HPLC peak area for the elimination product Me-**3** was corrected for the 7.0% of this alkene that was present as a contaminant of the substrate.

The products of the reactions of Me-**1**-(4-nitrobenzoate) ([S] = 1 mM) were analyzed after 5–20 halftimes for reaction of the substrate and were shown to be stable during this time.

Product studies for the relatively fast reactions of MeO-**1**-(4-methoxybenzoate) ([S] = 0.1–0.5 mM) were carried out at room temperature, 22 ± 2°C. It has been shown in previous work that there is no detectable difference between product ratios determined at room temperature and at 25°C (1, 14). For reactions in the absence of azide ion the products were analyzed after 20–70 halftimes for reaction of the substrate and were shown to be stable during this time. For reactions in the presence of azide ion the substrate concentration was at least 10-fold smaller than that of azide ion, in order to maintain pseudo-first-order conditions. For reactions at $[N_3^-]$ = 1–5 mM the azide ion adduct MeO-**1**-N_3 was unstable and the products were analyzed within the first 3 halftimes for reaction of the substrate, during which breakdown of MeO-**1**-N_3 is insignificant. For reactions at $[N_3^-] \geq 0.05$ M, the azide ion adduct Me-**1**-N_3 was stabilized by a common ion effect and the products were analyzed after 10–20 halftimes for reaction of the substrate. The substrate and the trifluoroethyl ether solvolysis product MeO-**1**-OCH_2CF_3 coeluted from the HPLC column. Therefore, for reactions that were analyzed before complete disappearance of the substrate, the total HPLC peak area for the solvent adducts was calculated with the assumption that the ratio of the HPLC peak areas for the solvolysis products MeO-**1**-OH and MeO-**1**-OCH_2CF_3 is the same as that determined in the absence of azide ion. In all cases, the HPLC peak area for the elimination product MeO-**3** was corrected for the 1.6% of this alkene that was present as a contaminant of the substrate.

HPLC analyses

Unless noted otherwise, the products of the reactions of X-**1**-Y were cleanly separated by reverse-phase HPLC as described previously (14, 15), with peak detection by a Waters 996 diode array detector. The products were detected by their UV absorbance at 280 nm for MeO-**1**-Y and at 269 nm for Me-**1**-Y and H-**1**-Y. These wavelengths are λ_{max} for the corresponding alcohols X-**1**-OH. The products of solvolysis and nucleophilic substitution by azide ion were identified as described previously (14, 15). The products of the elimination reactions of MeO-**1**-Y and Me-**1**-Y were identified as MeO-**3** and Me-**3**, respectively, by showing that their retention times were identical with those for authentic samples.

Ratios of product yields, $[P_1]/[P_2]$, were calculated using eq. [1], where A_1/A_2 is the ratio of the HPLC peak areas for the two products, and $\varepsilon_2/\varepsilon_1$ is the ratio of the molar extinction coefficients of the two products at the wavelength of the analysis.

$$[1] \qquad [P_1]/[P_2] = (A_1/A_2)(\varepsilon_2/\varepsilon_1)$$

Ratios of $\varepsilon_{\text{alkene}}/\varepsilon_{\text{ROH}} = (220\ M^{-1}\ cm^{-1})/(210\ M^{-1}\ cm^{-1}) = 1.0$ at 269 nm for Me-**3** and Me-**1**-OH and $\varepsilon_{\text{alkene}}/\varepsilon_{\text{ROH}} = (1270\ M^{-1}\ cm^{-1})/(860\ M^{-1}\ cm^{-1}) = 1.5$ at 280 nm for MeO-**3** and MeO-**1**-OH in 50:50 (v:v) methanol–water were determined using authentic materials. The extinction coefficients of the azide ion adduct Me-**1**-N_3 and the alkene Me-**3** at 269 nm were shown to be identical by comparison of the decrease in the HPLC peak area for the alkene and the increase in the sum of the peak areas of the solvent and azide ion adducts for reaction of a constant amount of substrate when the concentration of azide ion was increased from zero to 0.50 M. The extinction coefficients of the azide ion adduct MeO-**1**-N_3 and the alcohol MeO-**1**-OH at 280 nm were assumed to be identical because the extinction coefficients of the solvent and azide ion adducts to a wide range of α-substituted 4-methoxybenzyl carbocations are identical at λ_{max} for the corresponding alcohol (1). The extinction coefficients of the alcohols X-**1**-OH and trifluoroethyl ethers X-**1**-OCH_2CF_3 were assumed to be identical because it has been shown in previous work that the extinction coefficients of ring-substituted cumyl alcohols and trifluoroethyl ethers are identical at λ_{max} for the alcohols (4).

Calculation of product yields and rate constant ratios

Fractional yields of the solvolysis and elimination products of the reactions of X-**1**-Y were calculated as the ratio of the HPLC peak area for the product divided by the sum of the peak areas for all products, with correction where necessary for differences in the extinction coefficients of the various products (see above).

Dimensionless product rate constant ratios for the nucleophilic substitution reactions of water and trifluoroethanol with X-**1**-Y were calculated from the ratio of the yields of the corresponding alcohols and trifluoroethyl ethers using eq. [2]. Dimensionless product rate constant ratios for the partitioning of X-**1**-Y between solvolysis and elimination were calculated directly as the ratio of the yields of the products of these reactions using eq. [1].

$$[2] \qquad k_{\text{HOH}}/k_{\text{TFE}} = [\text{X-}\mathbf{1}\text{-OH}][CF_3CH_2OH]/[\text{X-}\mathbf{1}\text{-}OCH_2CF_3][HOH]$$

Rate constant ratios $k_{\text{az}}/k_{\text{s}}$ (M^{-1}) for the partitioning of Me-**1**-(4-nitrobenzoate) and MeO-**1**-(4-methoxybenzoate) between nucleophilic substitution by azide ion and solvent were calculated from the ratio of the yields of the azide ion and solvent adducts using eq. [3]. The values of $k_{\text{az}}/k_{\text{s}}$ (M^{-1}) determined at five or more values of $[N_3^-]$ agreed within the experimental error of ±10%.

$$[3] \qquad k_{\text{az}}/k_{\text{s}}\ (M^{-1}) = [\text{X-}\mathbf{1}\text{-}N_3]/(\textstyle\sum [\text{X-}\mathbf{1}\text{-OSolv}][N_3^-])$$

Kinetic methods

Kinetic studies were carried out in 50:50 (v:v) trifluoroethanol–water at 25°C and $I = 0.50$ ($NaClO_4$). Reactions were initiated by making a 100-fold dilution of a solution of substrate in acetonitrile into the appropriate reaction mixture. For reactions in the absence of azide ion, the solutions were buffered with 25 mM cacodylate, 80% anion, which prevented acid-catalyzed breakdown of the solvolysis products. Aqueous solutions containing sodium azide were adjusted to pH ≈7 with concentrated $HClO_4$ before use.

Rate constants for the reaction of MeO-**1**-(4-methoxybenzoate) ([S] = 0.1 mM) were determined spectrophotometrically by following the disappearance of the substrate at 270 nm or at 280 nm for reactions in the presence of azide ion. Rate constants for the reactions of Me-**1**-(4-nitrobenzoate) ([S] = 0.2 mM) were determined spectrophotometrically by following the increase in absorbance at 297 nm.

Rate constants for the reactions of Me-**1**-(4-methoxybenzoate) ([S] = 2 mM) and H-**1**-(4-methoxybenzoate) ([S] = 1 mM) were determined by following the disappearance of the substrate by HPLC, with peak detection at 285 nm. For Me-**1**-(4-methoxybenzoate) the reaction mixtures contained 9-methyl-9-fluorenol (1.7×10^{-5} M) as an internal HPLC injection standard. For H-**1**-(4-methoxybenzoate) the solution was unbuffered and contained 3-(4-methoxyphenyl)-1-propanol (4×10^{-4} M) as an internal HPLC injection standard.

In all cases, good first-order kinetics were observed over at least three reaction halftimes. First-order rate constants, k_{obsd}, were determined from the slopes of semilogarithmic plots of reaction progress against time. Rate constants determined spectrophotometrically were reproducible to ±5% and those determined by HPLC were reproducible to ±10%.

Results

Table 1 gives observed first-order rate constants, k_{obsd}, for the reactions of 4-substituted 2,6-dimethylcumyl derivatives X-**1**-Y in 50:50 (v:v) trifluoroethanol–water at 25°C and $I = 0.50$ ($NaClO_4$) that were determined by monitoring the reaction progress by UV spectroscopy or HPLC analysis, as described in the Experimental section. There was no significant change in k_{obsd} for the reactions of MeO-**1**-(4-methoxybenzoate), Me-**1**-(4-methoxybenzoate), and Me-**1**-(4-nitrobenzoate) when the concentration of azide ion was increased from zero to 0.50 M ($I = 0.50$, $NaClO_4$) (Table 1). The reactions of these substrates in the presence of 0.50 M azide ion result in the following good yields of the corresponding azide ion adducts: MeO-**1**-(4-methoxybenzoate), 93%; Me-**1**-(4-methoxybenzoate), 67%; Me-**1**-(4-nitrobenzoate), 68%.

Table 2 gives the yields of the solvolysis and elimination products of the reactions of MeO-**1**-Y and Me-**1**-Y in 50:50 (v:v) trifluoroethanol–water at $I = 0.50$ ($NaClO_4$) that were determined by HPLC analysis. The reaction mixtures were buffered with 25 mM cacodylate, 80% anion, which prevented acid-catalyzed breakdown of the solvolysis products X-**1**-OSolv to the alkenes X-**3**. In a control experiment, the yields of the products of the reaction of Me-**1**-(4-methoxybenzoate) in the absence of buffer determined during 10

Table 1. Observed first-order rate constants, k_{obsd} (s^{-1}), for the reactions of 4-substituted 2,6-dimethylcumyl derivatives X-**1**-Y in 50:50 (v:v) trifluoroethanol–water at 25°C and I = 0.50 (NaClO$_4$).[a]

	Leaving group Y	
Ring substituent X	4-Methoxybenzoate	4-Nitrobenzoate
MeO	5.8×10^{-3} [b] (5.5×10^{-3}) [c,d]	
Me	3.3×10^{-4} [e] (3.0×10^{-4}) [e,d]	3.2×10^{-3} [f] (2.9×10^{-3}) [f,d]
H	2.2×10^{-5} [e,d]	

[a] Determined in the presence of 25 mM cacodylate buffer, 80% anion, unless noted otherwise. Values in parentheses are for reaction in the presence of 0.50 M azide ion.

[b] Determined spectrophotometrically by following the disappearance of the substrate at 270 nm.

[c] Determined spectrophotometrically by following the disappearance of the substrate at 280 nm.

[d] Determined in unbuffered solution.

[e] Determined by following the disappearance of the substrate by HPLC.

[f] Determined spectrophotometrically by following the increase in absorbance at 297 nm.

Table 2. Yields of solvolysis and elimination products from the reactions of 4-substituted 2,6-dimethylcumyl derivatives X-**1**-Y in 50:50 (v:v) trifluoroethanol–water at I = 0.50 (NaClO$_4$).[a]

		Yield of product		
Ring substituent X	Leaving group Y	X-**1**-OH	X-**1**-OCH$_2$CF$_3$	X–**3**
MeO	4-Methoxybenzoate [b]	31.0%	1.8%	67.2%
Me	4-Methoxybenzoate [c]	13.1%	1.2%	85.7%
	4-Nitrobenzoate [d]	13.0%	1.3%	85.7%

[a] Determined in the presence of 25 mM cacodylate buffer, 80% anion, which prevented acid-catalyzed conversion of the solvent adducts to the alkenes. Product yields were determined by HPLC analysis.

[b] Product yields were determined at room temperature, 22 ± 2°C, after 20–70 halftimes for reaction of the substrate, and were stable during this time.

[c] Product yields were determined at 25°C after 2–30 halftimes for reaction of the substrate and were stable during this time.

[d] Product yields were determined at 25°C after 5–20 halftimes for reaction of the substrate and were stable during this time.

halftimes for reaction of the substrate were extrapolated to zero time. The absolute difference between the yields of Me-**1**-OSolv (14.6%) and Me-**3** (85.4%) obtained from this extrapolation and those determined in the presence of 25 mM cacodylate buffer (Table 2) is only 0.3%. The reaction of H-**1**-(4-methoxybenzoate) in 50:50 (v:v) trifluoroethanol–water at I = 0.50 (NaClO$_4$) gave a high yield of the alkene H-**3** along with the alcohol H-**1**-OH. The yield of H-**3** was not quantified, but this alkene represented ca. 94% of the total HPLC peak area of the products.

Table 3 gives the dimensionless product rate constant ratios k_{HOH}/k_{TFE} for partitioning of X-**1**-Y between nucleophilic substitution by water and trifluoroethanol in 50:50 (v:v) trifluoroethanol–water that were calculated from the ratio of the yields of the corresponding alcohols X-**1**-OH and trifluoroethyl ethers X-**1**-OCH$_2$CF$_3$ using eq. [2]. The dimensionless product rate constant ratios k_s/k_e for partitioning of X-**1**-Y between solvolysis and elimination (Table 3) were calculated directly as the ratio of the yields of the products of these reactions using eq. [1].

The products of the reactions of X-**1**-Y in 50:50 (v:v) trifluoroethanol–water in the presence of increasing concentrations of azide ion (I = 0.50, NaClO$_4$) were determined by HPLC analysis. Table 3 gives the rate constant ratios k_{az}/k_s (M^{-1}) for partitioning of MeO-**1**-(4-methoxybenzoate) and Me-**1**-(4-nitrobenzoate) between nucleophilic substitution by azide ion and solvent that were calculated from the ratio of the yields of the azide ion adducts X-**1**-N$_3$ and the solvent adducts X-**1**-OSolv using eq. [3]. For Me-**1**-(4-methoxybenzoate) the reaction products had to be analyzed at long reaction times, during which the azide ion adduct was unstable and broke down to give exalted yields of the solvolysis products (see Experimental section). Therefore, the value of k_{az}/k_s (M^{-1}) determined by direct product analysis was unreliable and this rate constant ratio was obtained from nonlinear least-squares analysis of the product data (see Discussion).

Figure 1 shows the effect of increasing concentrations of azide ion on the fractional yields of the nucleophilic substitution and elimination products of the reaction of MeO-**1**-(4-methoxybenzoate) in 50:50 (v:v) trifluoroethanol–water (I = 0.50, NaClO$_4$).

Figure 2 shows the effect of increasing concentrations of azide ion on the fractional yields of the nucleophilic substitution and elimination products of the reaction of Me-**1**-(4-nitrobenzoate) in 50:50 (v:v) trifluoroethanol–water (I = 0.50, NaClO$_4$). The yields of the azide ion adduct Me-**1**-N$_3$ and the alkene Me-**3** from these reactions agreed with those from the reaction of Me-**1**-(4-methoxybenzoate) under the same conditions, within the experimental error of ±10%.

Figure 3 shows the effect of increasing concentrations of acetate ion on the fractional yields of the nucleophilic substitution and elimination products of the reaction of Me-**1**-(4-methoxybenzoate) in the presence of 0.05 M azide ion in 50:50 (v:v) trifluoroethanol–water (I = 0.50, NaClO$_4$). In these experiments, the solutions were buffered with acetate, 95% anion, and there was no detectable formation of the acetate ion adduct.

Table 3. Rate constant ratios for partitioning of 4-substituted 2,6-dimethylcumyl carbocations X-**2** between nucleophilic addition and deprotonation in 50:50 (v:v) trifluoroethanol–water (Scheme 4).[a]

Ring substituent X	Leaving group[b]	$k_{\mathrm{HOH}}/k_{\mathrm{TFE}}$[c]	k_s/k_e[d]	k_{az}/k_s[e] (M^{-1})	k_{az}/k_e[f] (M^{-1})	k_{az}/k_B[g]
4-MeO	4-Methoxybenzoate	4.2	0.49	6200[h]	3000[i]	15.9[j]
4-Me	4-Methoxybenzoate	2.6	0.17	250[j]	42[j]	2.2[j]
	4-Nitrobenzoate	2.5	0.17	250[k]	42[i]	2.4[j]

[a] Determined in the presence of 25 mM cacodylate buffer, 80% anion, at 25°C and $I = 0.50$ ($NaClO_4$), unless noted otherwise. Product yields for MeO-**1**-(4-methoxybenzoate) were determined at room temperature, 22 ± 2°C.

[b] Leaving group at X-**1**-Y that was used to generate the corresponding carbocation X-**2**.

[c] Dimensionless ratio of second-order rate constants, calculated from the ratio of the yields of the alcohol and the trifluoroethyl ether using eq 2.

[d] Dimensionless ratio of first-order rate constants, calculated as the ratio of the yields of the solvent adducts X-**1**-OSolv and the alkene X-**3** in the absence of azide ion (Table 2) using eq. [1].

[e] Rate constant ratio for partitioning of the carbocation between nucleophilic addition of azide ion and solvent, calculated from the ratio of the yields of the azide ion and solvent adducts using eq. [3], unless noted otherwise.

[f] Rate constant ratio for partitioning of the carbocation between nucleophilic addition of azide ion and deprotonation by solvent.

[g] Dimensionless ratio of second-order rate constants for reaction of the carbocation with azide ion as a Lewis and a Brønsted base.

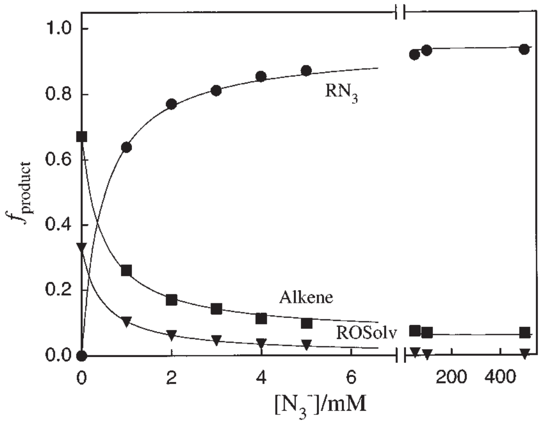
[h] Average of values determined at five concentrations of azide ion in the range 0.001–0.005 M.

[i] Calculated as $(k_{az}/k_s)(k_s/k_e)$.

[j] Determined from the nonlinear least-squares fit of the product data to eqs. [4] and [5], see text.

[k] Average of values determined at eight concentrations of azide ion in the range 0.005–0.300 M.

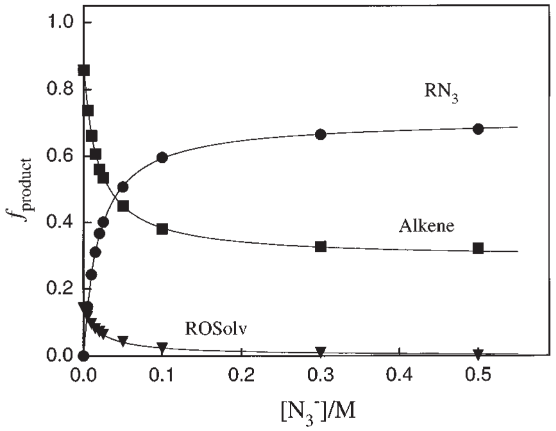
Fig. 1. Dependence of the fractional yields of the azide ion adduct MeO-**1**-N_3 (●), the solvent adducts MeO-**1**-OSolv (▼), and the alkene MeO-**3** (■) from the reaction of MeO-**1**-(4-methoxybenzoate) on the concentration of azide ion in 50:50 (v:v) trifluoroethanol–water at room temperature, 22 ± 2°C, and $I = 0.50$ ($NaClO_4$). For $[N_3^-] \leq 0.05$ M the solutions were buffered with 25 mM cacodylate, 80% anion. The solid lines show the nonlinear least-squares fits of the data to eqs. [4]–[6] (see text).



Discussion

In 50:50 (v:v) trifluoroethanol–water ($I = 0.50$, $NaClO_4$) the ring-substituted 2,6-dimethylcumyl derivatives X-**1**-Y undergo nucleophilic substitution by solvent to give the corresponding alcohols X-**1**-OH and trifluoroethyl ethers X-**1**-OCH_2CF_3 (Table 2). However, the major products of the reactions of X-**1**-Y are those of elimination, the alkenes X-**3** (Table 2). The yield of the alkene X-**3** increases as the ring substituent at X-**1**-Y is made more electron withdrawing, from 67% for MeO-**1**-(4-methoxybenzoate) to 86% for Me-**1**-(4-methoxybenzoate) and Me-**1**-(4-nitrobenzoate) (Table 2).

Fig. 2. Dependence of the fractional yields of the azide ion adduct Me-**1**-N_3 (●), the solvent adducts Me-**1**-OSolv (▼), and the alkene Me-**3** (■) from the reaction of Me-**1**-(4-nitrobenzoate) on the concentration of azide ion in 50:50 (v:v) trifluoroethanol–water at 25°C and $I = 0.50$ ($NaClO_4$). For $[N_3^-] \leq 0.05$ M the solutions were buffered with 25 mM cacodylate, 80% anion. The solid lines show the nonlinear least-squares fits of the data to eqs. [4]–[6] (see text).



Reaction mechanism

We have shown previously that the nucleophilic substitution reactions of ring-substituted cumyl 4-nitrobenzoates ($XC_6H_4CMe_2$(4-nitrobenzoate)) and the acid-catalyzed reactions of ring-substituted cumyl alcohols ($XC_6H_4CMe_2OH$) in 50:50 (v:v) trifluoroethanol–water proceed by a stepwise mechanism through cumyl carbocation intermediates, $XC_6H_4CMe_2^+$. The reactions of the 2,6-dimethylcumyl derivatives MeO-**1**-Y and Me-**1**-Y in 50:50 (v:v) trifluoroethanol–water in the presence of 0.50 M azide ion give good yields (≥67%) of the azide ion adducts X-**1**-N_3 at the expense of both the solvent adducts X-**1**-OSolv and the alkenes X-**3** (Figs. 1 and 2). The absence of any increases in k_{obsd} for these reactions in the presence of azide ion (Table 1), and the identical yields of the substitution and elimination products from the reactions of Me-**1**-(4-methoxybenzoate) and

Scheme 2.

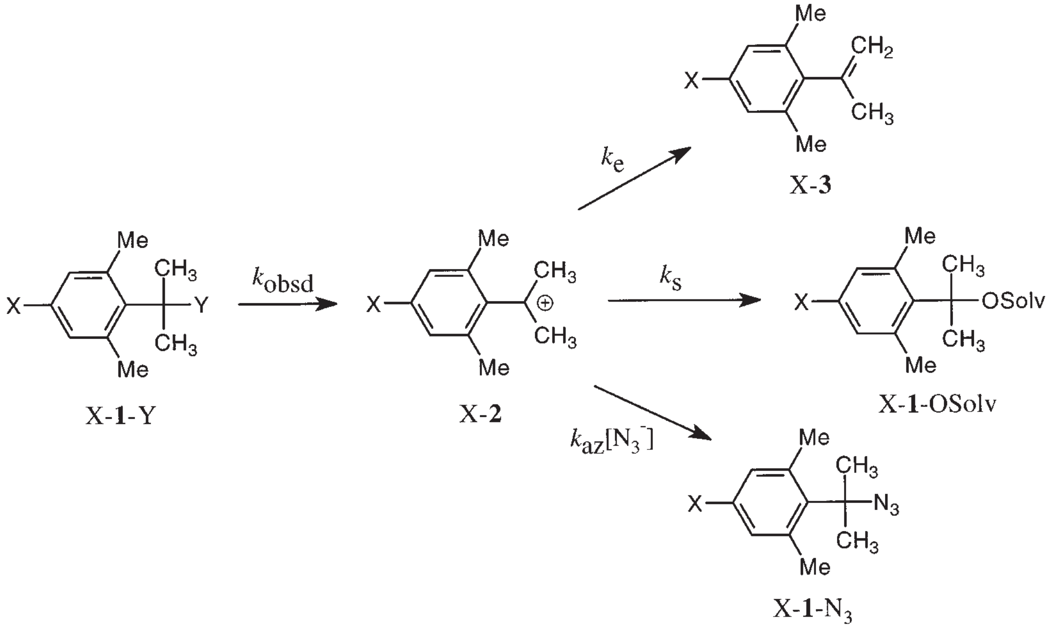
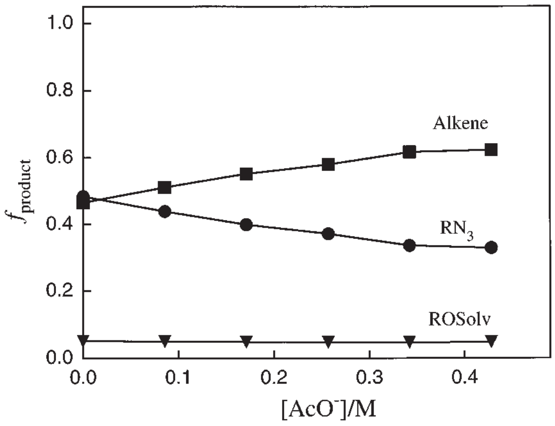


Fig. 3. Dependence of the fractional yields of the alkene Me-**3** (■), the azide ion adduct Me-**1**-N_3 (●), and the solvent adducts Me-**1**-OSolv (▼) from the reaction of Me-**1**-(4-methoxybenzoate) on the concentration of acetate ion in the presence of 0.05 M azide ion in 50:50 (v:v) trifluoroethanol–water at 25°C and I = 0.50 ($NaClO_4$). The solutions were buffered with acetate, 95% anion.



Me-**1**-(4-nitrobenzoate), which have different leaving groups, provide strong evidence that X-**1**-Y also react by a stepwise $D_N + A_N$ (S_N1) (16) mechanism through the liberated 2,6-dimethylcumyl carbocations X-**2** (Scheme 2). Similarly, the elimination reactions of H-**1**-(trifluoroacetate) in acetic acid and trifluoroethanol have been reported to proceed by a stepwise mechanism through the 2,6-dimethylcumyl carbocation H-**2**, which undergoes proton loss to give the alkene H-**3** as the sole product (5). Therefore, the rate constant ratios k_{az}/k_s (M^{-1}) and k_s/k_e for the reactions of X-**1**-Y that were determined by product analysis (Table 3) represent rate constant ratios for partitioning of the 2,6-dimethylcumyl carbocation intermediates X-**2** between nucleophilic addition of azide ion and solvent to the benzylic carbon, and nucleophilic addition of solvent and deprotonation, respectively (Scheme 2).

Effect of *ortho*-methyl groups on the formation of cumyl carbocations

The effects of *ortho* substituents on the reactivity of aromatic substrates are difficult to interpret because their close proximity to the reaction site may result in gross changes in the energy of the ground state and (or) the transition state that are not related to the polar and resonance effects of these substituents (6–8).

Table 4 gives relative rate constants for the stepwise reactions of ring-substituted cumyl 4-nitrobenzoates (data from previous work (1)[2]) and the corresponding 2,6-dimethylcumyl 4-nitrobenzoates (data from this work) in 50:50 (v:v) trifluoroethanol–water. The data show that the addition of a pair of *ortho*-methyl groups to $XC_6H_4CMe_2Y$ results in relatively small (<5-fold) changes in the rate constant for cleavage of the substrate to give the corresponding carbocation. This is surprising, because the simple expectation is that *ortho*-methyl substituents should result in large increases in the rate constant for carbocation formation, as a result of both electron donation from the *ortho* methyl groups and increased steric crowding at the sp^3-hybridized benzylic carbon in the ground state that is relieved on moving towards sp^2-hybridization in the transition state. A crude analysis, based on the assumption that the effect of each *ortho*-methyl group is the same as that of a 4-Me group at $XC_6H_4CMe_2Y$, suggests that formation of the 2,4,6-trimethylcumyl carbocation Me-**2** from Me-**1**-Y should be ca. $(40)^2$ = 1600-fold faster than the formation of $4\text{-}MeC_6H_4CMe_2^+$ from $4\text{-}MeC_6H_4CMe_2Y$. However, although the solvolyses of both benzyl chloride and 1-phenylethyl chloride are accelerated by the addition of an *ortho*-methyl group, for both compounds the effect is ca. 2-fold smaller than the effect of a 4-Me group (17). This suggests that any steric or other un-

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[2] T.L. Amyes. Unpublished results.

Table 4. Relative rate constants, k_{rel}, for the reactions of ring-substituted cumyl 4-nitrobenzoates and the corresponding 2,6-dimethylcumyl 4-nitrobenzoates in 50:50 (v:v) trifluoroethanol–water.[a]

Ring substituent	k_{rel} Cumyl	k_{rel} 2,6-Dimethylcumyl	2,6-Me_2/2,6-H_2[b]
4-MeO	1840[c]	1150[d]	0.63
4-Me	39[e]	65[f]	1.7
4-H	1	4.4[d]	4.4

[a] At 25°C and I = 0.50 ($NaClO_4$). Relative rate constants are normalized to $k_{obsd} = 4.9 \times 10^{-5}$ s^{-1} for the reaction of cumyl 4-nitrobenzoate that was determined by interpolation of the data in Fig. 4 (T. L. Amyes. Unpublished results).

[b] Ratio of rate constants for reaction of 2,6-dimethylcumyl and cumyl 4-nitrobenzoates with the same aromatic ring substituent.

[c] $k_{obsd} = 0.09$ s^{-1} (1).

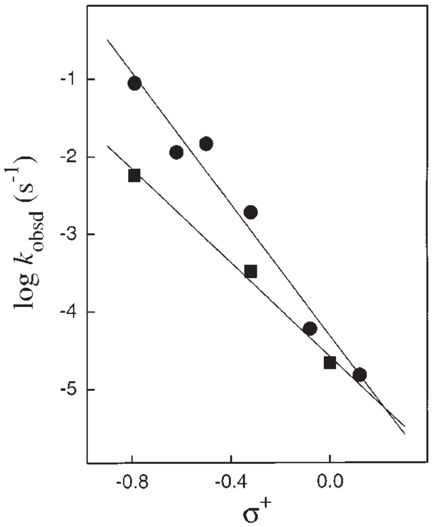
[d] Calculated from data for 2,6-dimethylcumyl 4-methoxybenzoates (Table 1) with the assumption that the change to a 4-nitrobenzoate leaving group results in the same 9.7-fold increase in k_{obsd} as that observed for Me-**1**-(4-methoxybenzoate) (Table 1).

[e] $k_{obsd} = 1.9 \times 10^{-3}$ s^{-1} (T.L. Amyes. Unpublished results).

[f] Calculated from data in Table 1.

usual *ortho* effects (6–8) associated with the addition of a single *ortho*-methyl group to 1-phenylethyl chloride are small. Therefore, if the effects of *ortho*-methyl groups at $XC_6H_4CMe_2Y$ are additive, the cleavage of Me-**1**-Y to give Me-**2** is expected to be $(40/2)^2$ = 400-fold faster than the cleavage of 4-$MeC_6H_4CMe_2Y$ to give 4-$MeC_6H_4CMe_2^+$. The observation that the formation of Me-**2** is only 1.7-fold faster than the formation of 4-$MeC_6H_4CMe_2^+$ (Table 4) suggests there is an offsetting 240-fold *decrease* in the rate of carbocation formation due to an *ortho* effect. Similar analyses for the formation of MeO-**2** and H-**2** suggest that the cleavage reactions of MeO-**1**-Y and H-**1**-Y are 630-fold and 90-fold slower, respectively, than expected on the basis of additivity of the effects of *ortho*-methyl groups. The origin of these large effects is undoubtedly adverse steric interactions between the *ortho*-methyl groups and the α-methyl groups at the benzylic carbon in the carbocations X-**2** and in the transition state leading to their formation. These steric interactions are expected to lead to significant decreases in coplanarity and overlap of the π-orbitals of the aromatic ring with the empty *p*-orbital at the benzylic carbon of X-**2**, resulting in a decrease in the resonance stabilization of X-**2** and increases in the energy of both these carbocations and the transition state leading to their formation. Such effects have long been recognized and termed "steric inhibition of resonance" (11, 18). Consistent with this, the addition of a pair of *ortho*-methyl groups to the less sterically congested 1-phenylethyl derivatives should result in a smaller degree of "steric inhibition," and the solvolysis of 1-(2,4,6-trimethylphenyl)ethyl chloride is only 5-fold slower than expected on the basis of additivity of the effects of *ortho*-methyl groups at 4-$MeC_6H_4CH(Me)Cl$ (17).

Fig. 4. Logarithmic correlations of observed first-order rate constants, k_{obsd} (s^{-1}), for the reactions of ring-substituted cumyl 4-nitrobenzoates (●, data from previous work $(1)^2$) and 4-substituted 2,6-dimethylcumyl 4-methoxybenzoates (■, data from Table 1) in 50:50 (v:v) trifluoroethanol–water at 25°C and I = 0.50 ($NaClO_4$) with Hammett σ^+ substituent constants (19). The slopes of the plots give $\rho^+ = -4.3$ for cumyl 4-nitrobenzoates and $\rho^+ = -3.0$ for 2,6-dimethylcumyl 4-methoxybenzoates.

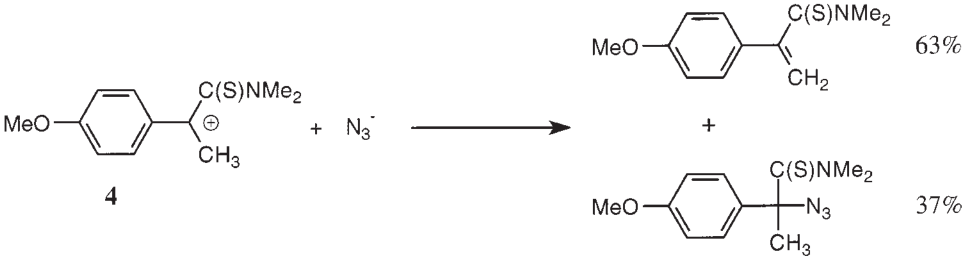


Structure–reactivity correlations

The data in Table 4 show that there is a 7-fold decrease in the *relative* rate constant for cleavage of X-**1**-Y and the corresponding $XC_6H_4CMe_2Y$ in 50:50 (v:v) trifluoroethanol–water as the aromatic substituent X is made more electron donating. In fact, the addition of two electron-donating *ortho*-methyl groups to 4-$MeOC_6H_4CMe_2Y$ to give MeO-**1**-Y actually leads to a 1.6-fold *decrease* in the rate constant for cleavage of the substrate to give the corresponding carbocation! Figure 4 shows the Hammett correlation of k_{obsd} for the reaction of ring-substituted cumyl 4-nitrobenzoates in 50:50 (v:v) trifluoroethanol–water (data from previous work $(1)^2$) with σ^+ substituent constants (19) and the correlation of the more limited set of data from this work for the reactions of 2,6-dimethylcumyl 4-methoxybenzoates in the same solvent (Table 1). The data are correlated by $\rho^+ = -4.3$ for the reactions of $XC_6H_4CMe_2$(4-nitrobenzoate) and by a somewhat smaller value of $\rho^+ = -3.0$ for the reactions of X-**1**-(4-methoxybenzoate). Decreased Hammett ρ values and small Yukawa–Tsuno *r* values have been observed for the solvolysis reactions of benzyl derivatives substituted with very bulky alkyl groups at the α-carbon (20).

The substantial negative value of $\rho^+ = -3.0$ for the reactions of X-**1**-Y shows that, despite the above estimated 630-fold decrease in the rate constant for formation of MeO-**2** resulting from decreased overlap between the π-orbitals of the aromatic ring and the developing empty p-orbital at the benzylic carbon, the 4-MeO group results in a significant 3.3 kcal/mol stabilization of the transition state for carbocation formation from X-**1**-Y (Table 4). For the corresponding simple cumyl system, the addition of a 4-MeO group results in stabilization of the transition state for carbocation formation by 4.4 kcal/mol (Table 4). Therefore, only 25% of the stabilization of the transition state for formation of $XC_6H_4CMe_2^+$ from $XC_6H_4CMe_2Y$ by resonance delocalization of positive charge at the benzylic carbon onto the 4-MeO group is lost as a result of the increased steric requirements of the *ortho*-methyl groups in the transition state for formation of X-**2** from X-**1**-Y. The crystal structure of

Scheme 3.



$C_6H_5CMe_2^+\cdot SbF_6^-$ shows that the cumyl carbocation is almost completely planar: the aromatic ring is twisted out of the plane of the benzylic carbon by only 8° (21). By contrast, the small value of λ_{max} for the 2,4,6-trimethylcumyl carbocation suggests that there is considerable twisting about the bond between the aromatic ring and the benzylic carbon in this carbocation (11). Our results suggest that, despite the nonplanar structures of X-**2**, electron-donating aromatic substituents can provide substantial resonance stabilization of these carbocations.

Mechanism of elimination reactions of *ortho*-dimethylcumyl derivatives

Figures 1 and 2 show that the addition of azide ion results in the formation of good yields of the azide ion adducts X-**1**-N_3 from the stepwise reactions of MeO-**1**-(4-methoxybenzoate) and Me-**1**-(4-nitrobenzoate) in 50:50 (v:v) trifluoroethanol–water (I = 0.50, $NaClO_4$). At high concentrations of azide ion, the yields of the solvent adducts X-**1**-OSolv approach zero, as required by the mechanism shown in Scheme 2. By contrast, the yields of the alkenes decrease to essentially constant limiting values of 7% MeO-**3** from the reaction of MeO-**1**-(4-methoxybenzoate) (Fig. 1) and 32% Me-**3** from the reactions of Me-**1**-(4-nitrobenzoate) (Fig. 2) and Me-**1**-(4-methoxybenzoate) (data not shown). The simple mechanism shown in Scheme 2, in which the solvent and azide ion adducts and the alkenes are formed by partitioning of a common carbocation intermediate, requires that, like the solvent adducts, the yields of the alkenes also approach zero in the presence of high concentrations of azide ion. However, the results show that only 93% of the reaction of MeO-**1**-Y and 68% of the reaction of Me-**1**-Y proceed through the liberated carbocation intermediate X-**2** that can be trapped by nucleophilic addition of azide ion. The remainder proceeds through an additional pathway that results in formation of the alkenes X-**3**. There are several mechanistic possibilities for this additional pathway for the elimination reactions of X-**1**-Y to give the alkenes X-**3**.

Mechanism 1: The substrates X-1-Y undergo concerted elimination

The constant limiting yields of the alkenes X-**3** in the presence of high concentrations of azide ion may result from a concerted elimination reaction of X-**1**-Y that bypasses the carbocation intermediate of the stepwise reaction and has an observed rate constant that is independent of the concentration of added azide ion (3). This possibility can be excluded because the quantitative elimination reaction of H-**1**-(trifluoroacetate) in acetic acid has been shown to proceed by a stepwise mechanism through the carbocation H-**2** (5). The change in solvent from acetic acid (Y = –1.64) (22) to the more ionizing solvent of 50:50 (v:v) trifluoroethanol–water ($Y \approx 2.0$)[3] used in this work is expected to increase rather than decrease the importance of the stepwise reaction pathway through the carbocations X-**2**.[4]

Mechanism 2: The carbocations X-2 undergo proton transfer to the leaving group within an ion pair intermediate

The carbocation-leaving group ion-pair intermediates of the reactions of ring-substituted cumyl derivatives are too shortlived to undergo trapping by azide ion because they undergo fast diffusional separation to give the free ions (24, 25). Therefore, any proton transfer from the carbocation to the leaving group within the ion pairs X-**2**·Y^- would provide a pathway for formation of the alkenes X-**3** that is insensitive to added azide ion. The yields of α-methylstyrenes from the ion-pair intermediates of the reactions of ring-substituted cumyl 4-nitrobenzoates with electron-donating substituents are negligible (3). Therefore, this possibility would require that the addition of a pair of *ortho*-methyl groups to ring-substituted cumyl derivatives result in a large increase in the rate constant for proton transfer from the carbocation to the leaving group within an ion pair, relative to that for diffusional separation of the ion pair to give the free carbocation. It is difficult to exclude rigorously the formation of small amounts of the alkenes X-**3** from deprotonation within an ion-pair intermediate. However, the observation of identical limiting yields of 32% Me-**3** from the reactions of Me-**1**-(4-nitrobenzoate) and Me-**1**-(4-methoxybenzoate) with leaving groups of different basicities provides strong evidence against the formation of large amounts of Me-**3** from proton transfer to the leaving group within an ion-pair intermediate.

Mechanism 3: The carbocations X-2 react with azide ion as both a Brønsted and a Lewis base

Azide ion usually undergoes reaction with α-methylbenzyl carbocations exclusively as a nucleophile (Lewis base). However, we have recently shown that the α-thioamide substituted 4-methoxybenzyl carbocation **4** reacts with azide ion in 50:50 (v:v) methanol–water predominantly as a Brønsted

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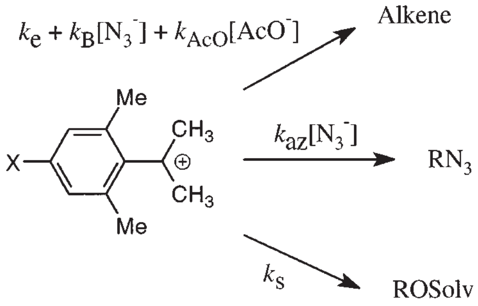
[3] Calculated by linear interpolation of the values of Y = 2.23 and 1.89 for 50:50 (w:w) and 60:40 (w:w) trifluoroethanol–water, respectively (23), to 58:42 (w:w) trifluoroethanol–water which corresponds to 50:50 (v:v) trifluoroethanol–water.

[4] A change to a more ionizing solvent results in a smaller increase in the rate constant for concerted pericyclic elimination of simple cumyl derivatives with electron-withdrawing ring substituents than in the rate constant for the concurrent solvolysis reaction (3).

Scheme 4.



base (63% deprotonation) rather than a Lewis base (37% nucleophilic addition, Scheme 3) (2). In the absence of azide ion, **4** undergoes loss of a proton to solvent to give the corresponding alkene as the only detectable product (k_s/k_e ≤0.01) (2). This surprising reactivity of azide ion as a Brønsted base was attributed to the large stability of the corresponding α-thioamide substituted alkene relative to the nucleophile adducts, and the resulting strong tendency of **4** to undergo loss of a proton rather than nucleophilic capture (2).

The values of $k_s/k_e = 0.49$ for partitioning of MeO-**2** and $k_s/k_e = 0.17$ for partitioning of Me-**2** in 50:50 (v:v) trifluoroethanol–water (Table 3) are much smaller than k_s/k_e >100 for the partitioning of simple cumyl carbocations $XC_6H_4CMe_2^+$ between addition of solvent to the benzylic carbon and deprotonation in the same solvent (3, 4). Therefore, the 2,6-dimethylcumyl carbocations X-**2** also show an unusual tendency to undergo loss of a proton to solvent rather than nucleophilic capture at the benzylic carbon. We propose that the constant limiting yields of the alkenes X-**3** observed in the presence of high concentrations of azide ion result from reaction of azide ion with the carbocations X-**2** as a Brønsted rather than a Lewis base (k_B, Scheme 4).

The solid lines in Figs. 1 and 2 show that there is a good fit of the observed product yields for the reactions of MeO-**1**-(4-methoxybenzoate) and Me-**1**-(4-nitrobenzoate) to eqs. [4]–[6], which were derived for the mechanism shown in Scheme 4, using the values of k_s/k_e and k_{az}/k_e (M^{-1}) = $(k_{az}/k_s)(k_s/k_e)$ that were determined directly from product analysis (Table 3). The nonlinear least-squares fits of the product data to eqs. [4] and [5] gave $k_B/k_e = 191 \pm 12$ M^{-1} and 17.4 ± 0.2 M^{-1} for the partitioning of MeO-**2** and Me-**2** between deprotonation by azide ion and by solvent, respectively. These rate constant ratios were combined with the values of k_{az}/k_e (M^{-1}) to give values of $k_{az}/k_B = (k_{az}/k_e)(k_e/k_B)$ for partitioning of X-**2** between reaction with azide ion as a nucleophile and as a Brønsted base (Table 3). For the reactions of Me-**1**-(4-methoxybenzoate), the value of k_{az}/k_s (M^{-1}) determined directly from product analysis was unreliable (see Results). Therefore the product data were fitted to eqs. [4] and [5] using the only the observed value of k_s/k_e (Table 3) to give values of $k_{az}/k_e = 42$ M^{-1}, $k_B/k_e = 19$ M^{-1}, and $k_{az}/k_s = (k_{az}/k_e)(k_e/k_s) = 250$ M^{-1}, which are in good agreement with those for partitioning of Me-**2** generated from the cleavage of Me-**1**-(4-nitrobenzoate) (Table 3).

$$[4] \qquad f_{alk} = \frac{1 + (k_B/k_e)[N_3^-]}{1 + (k_s/k_e) + (k_B/k_e + k_{az}/k_e)[N_3^-]}$$

$$[5] \qquad f_{az} = \frac{(k_{az}/k_e)[N_3^-]}{1 + (k_s/k_e) + (k_B/k_e + k_{az}/k_e)[N_3^-]}$$

$$[6] \qquad f_{solv} = \frac{(k_s/k_e)}{1 + (k_s/k_e) + (k_B/k_e + k_{az}/k_e)[N_3^-]}$$

The rate constant ratio for partitioning of the α-thioamide substituted 4-methoxybenzyl carbocation **4** between reaction with azide ion as a nucleophile and a Brønsted base, k_{az}/k_B = 0.59 (2), is 27-fold smaller than $k_{az}/k_B = 15.9$ for the presumably much more hindered carbocation MeO-**2**. This suggests that the unusual reactivity of azide ion as Brønsted base for deprotonation of X-**2** is not due simply to steric hindrance to nucleophilic attack at the benzylic carbon, because this should be less favored for MeO-**2** than for **4**.

The pK_a's of acetic acid (4.76) and hydrazoic acid (4.72) are similar (26), so that acetate and azide ions would be expected to show similar reactivities as Brønsted bases for deprotonation of X-**2**. We determined the relative reactivity of azide and acetate ions as general bases for the deprotonation of Me-**2** from the effect of increasing concentrations of acetate ion (0.086–0.430 M) on the product distribution for the reaction of Me-**1**-(4-methoxybenzoate) in 50:50 (v:v) trifluoroethanol–water in the presence of a fixed concentration of azide ion (0.05 M) at $I = 0.50$ ($NaClO_4$). Figure 3 shows that increases in the concentration of acetate ion result in increases in the fractional yield of the alkene Me-**3** at the expense of the azide ion adduct Me-**1**-N_3. The constant yields of the solvent adducts Me-**1**-OSolv in the presence of increasing concentrations of acetate ion is not expected on the basis of the mechanism of Scheme 4, but it can be attributed to general base catalysis by acetate ion of the nucleophilic addition of solvent to the carbocation (27, 28). Acetate ion is less nucleophilic towards carbocations than azide ion (14) and there was no detectable formation of the acetate ion adduct in these experiments. Conversely, the very high reactivity of azide ion as a nucleophile towards unstable carbocations (29, 30) precludes the observation of general base catalysis by azide ion of the addition of solvent to Me-**2**. Figure 5 shows that the *ratio* of the fractional yields of the alkene Me-**3** and the azide ion adduct Me-**1**-N_3 formed in these experiments, f_{alk}/f_{az}, shows a linear dependence on the concentration of added acetate ion, according to eq. [7], derived for the mechanism shown in Scheme 4. The solid line through the data in Fig. 5 is the least-squares fit to eq. [7] with slope $(k_{AcO}/k_{az}[N_3^-]) = 2.29$ M^{-1} ($r = 0.992$), which gives $k_{AcO}/k_{az} = (2.29\ M^{-1} \times 0.05\ M) = 0.115$. This was combined with the average value of $k_{az}/k_B = 2.3$ from Table 3 to give $k_B/k_{AcO} = 3.8$ as the relative reactivities of azide and acetate ions as Brønsted bases for deprotonation of Me-**2**. A very similar 4.5-fold greater reactivity of azide than of acetate ion was determined for deprotonation of the α-thioamide substituted 4-methoxybenzyl carbocation **4** (2).

$$[7] \qquad f_{alk}/f_{az} = \left(\frac{k_B[N_3^-] + k_e}{k_{az}[N_3^-]}\right) + \left(\frac{k_{AcO}}{k_{az}[N_3^-]}\right)[AcO^-]$$

Table 5. Rate constants for nucleophilic addition and proton transfer reactions of 4-substituted 2,6-dimethylcumyl carbocations X-**2** and the 4-methylcumyl carbocation in 50:50 (v:v) trifluoroethanol–water at 25°C and I = 0.50 ($NaClO_4$) (Scheme 4).

Carbocation	k_{az} (M^{-1} s^{-1})	k_B (M^{-1} s^{-1})	k_s (s^{-1})	k_e (s^{-1})
MeO-**2** [a]	$\leq 4.7 \times 10^9$	$\leq 3.0 \times 10^8$	$\leq 7.6 \times 10^5$	$\leq 1.6 \times 10^6$
Me-**2** [b]	3.5×10^9	1.5×10^9	1.4×10^7	8.3×10^7
$4\text{-MeC}_6H_4CMe_2+$	5.0×10^9		1×10^9 [c]	1.4×10^6 [d]

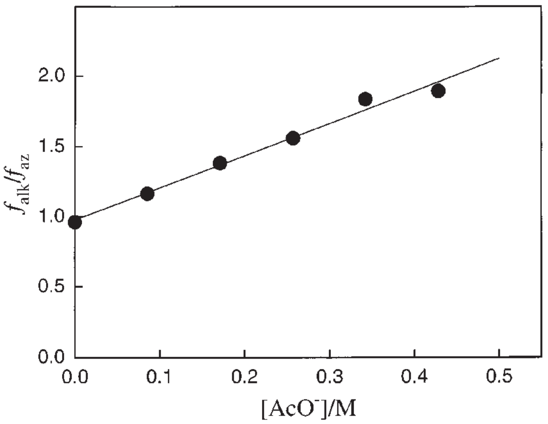
[a] At room temperature 22 ± 2°C. Rate constants are upper limits calculated from the rate constant ratios in Table 3 using values of (k_{az} + k_B) ≤ 5 × 10^9 M^{-1} s^{-1} and k_{az}/k_B = 15.9, see text.

[b] Calculated from the rate constant ratios in Table 3 using (k_{az} + k_B) = 5 × 10^9 M^{-1} s^{-1} and the average value of k_{az}/k_B = 2.3, see text.

[c] Calculated from k_{az}/k_s = 5 M^{-1} (31) and k_{az} = 5 × 10^9 M^{-1} s^{-1} for the diffusion limited reaction of azide ion with unstable carbocations, see text.

[d] Calculated from k_e/k_s = 0.0014 determined from product analysis of the acid-catalyzed cleavage of 4-methylcumyl methyl ether (T. L. Amyes. Unpublished results).

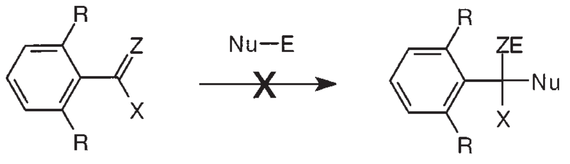
Fig. 5. Dependence of the ratio of the fractional yields of the alkene Me-**3** and azide ion adduct Me-**1**-N_3 from the reaction of Me-**1**-(4-methoxybenzoate), f_{alk}/f_{az}, on the concentration of acetate ion in the presence of 0.05 M azide ion in 50:50 (v:v) trifluoroethanol–water at 25°C and I = 0.50 ($NaClO_4$). The solutions were buffered with acetate, 95% anion. The solid line shows the least-squares fit of the data to eq. [7]. The slope of this line is $k_{AcO}/k_{az}[N_3^-]$ = 2.29 M^{-1} (r = 0.992) for partitioning of the carbocation Me-**2** between deprotonation by acetate ion and nucleophilic addition of azide ion (see text).



Effect of *ortho*-methyl groups on the reactions of cumyl carbocations

The azide ion selectivities k_{az}/k_s (M^{-1}) for nucleophilic capture of the 2,6-dimethylcumyl carbocations MeO-**2** and Me-**2** by azide ion and a solvent of 50:50 (v:v) trifluoroethanol–water (Table 3) are significantly larger than the corresponding values of k_{az}/k_s = 380 M^{-1} (1, 31) and 5 M^{-1} (31) for the corresponding simple cumyl carbocations $4\text{-MeOC}_6H_4CMe_2^+$ and $4\text{-MeC}_6H_4CMe_2^+$, respectively, which shows that X-**2** are moderately selective carbocations. The reaction of azide ion with a range of unstable α-substituted 4-methoxybenzyl carbocations in 98:2 (v:v) trifluoroethanol–water is diffusion controlled, with k_{az} = 5 × 10^9 M^{-1} s^{-1} (29), and the rate constant for reaction of azide ion with ring-substituted triarylmethyl carbocations in 1:2 (v:v) acetonitrile–water does not drop significantly below this value until the azide/solvent selectivities become larger than $k_{az}/k_s \approx 10^4$ M^{-1} (30). This diffusion-limited reaction of azide ion with carbocations acts as a “clock” for other reactions of the carbocation (15, 32, 33). Therefore, the values of k_{az}/k_B, k_{az}/k_s (M^{-1}), and k_{az}/k_e (M^{-1}) for the partitioning of Me-**2** (Table 3) can be combined with (k_{az} + k_B) = 5 × 10^9 M^{-1} s^{-1} for the diffusion-controlled reaction of azide ion (29, 30) to give the absolute values of k_B, k_s, and k_e for the reactions of Me-**2** given in Table 5. The large value of k_{az}/k_s = 6200 M^{-1} for partitioning of MeO-**2** is approaching the azide/solvent selectivity at which the reactions of triarylmethyl carbocations with azide ion drop below the diffusion limit, and a value of k_{az} = 4 × 10^9 M^{-1} s^{-1} has been determined for the reaction of azide ion with $4\text{-MeOC}_6H_4CMe_2^+$ (29). Therefore, the partitioning ratios for MeO-**2** (Table 3) were combined with (k_{az} + k_B) ≤5 × 10^9 M^{-1} s^{-1} to give the upper limits on the absolute rate constants for the reactions of MeO-**2** given in Table 5.

Scheme 5.



5 **6**

The data in Table 5 show that the effect of the pair of *ortho*-methyl groups on the *overall* reactivity of Me-**2** is small: a 10-fold decrease in (k_s + k_e) compared with the simple 4-methylcumyl carbocation. However, the addition of a pair of *ortho*-methyl groups to $4\text{-MeC}_6H_4CMe_2^+$ to give Me-**2** results in a larger 70-fold decrease in k_s for nucleophilic capture by solvent of the carbocation at the benzylic carbon (Table 5) and a 60-fold *increase* in k_e for deprotonation of the carbocation by solvent. The steric requirements of proton transfer from the β-carbon of Me-**2** should be similar to those for deprotonation of $4\text{-MeC}_6H_4CMe_2^+$. Therefore, the greater reactivity of Me-**2** than of $4\text{-MeC}_6H_4CMe_2^+$ towards proton transfer suggests that, relative to the corresponding alkenes, 2,6-dimethylcumyl carbocations are intrinsically less stable than simple cumyl carbocations. This decreased stability of X-**2** relative to X-**3** is very likely due to a nonplanar conformation of these species in which overlap between the π-orbitals of the aromatic ring and the *p*-orbital at the sp^2-hybridized benzylic carbon is decreased relative to that at $XC_6H_4CMe_2^+$ and ring-substituted α-methylstyrenes. This would tend to increase the energy of X-**2** relative to X-**3**, because there is more demand for resonance stabilization of the positive charge at the benzylic carbon of X-**2** than of the alkene double bond at X-**3**. The very low extinction coefficient of Me-**3** (220 M^{-1} cm^{-1}, this work) provides strong evidence that the alkene double bond is twisted out of the plane of the aromatic ring by a considerable amount (34), and the UV spectrum of Me-**3** resembles that of benzene rather than an α-methylstyrene (11).

Formation of *ortho*-methyl cumyl derivatives

The very large yield of 93% of the products of nucleophilic substitution from the reaction of MeO-**1**-(4-methoxybenzoate) in the presence of high concentrations of azide ion (Fig. 1) represents, to the best of our knowledge, the first example of the formation of stable products of the addition of nucleophiles to disubstituted sp^2-hybridized carbon attached to a 2,6-disubstituted aryl moiety. Compounds of general structure **5** are known to be extremely unreactive (35) and 2,6-disubstituted α-methylstyrenes (**5**, $X = CH_3$, $Z = CH_2$) are inert to addition across the olefinic double bond (11, 12) (Scheme 5). For example, Me-**3** reacts with bromine to give the products of electrophilic substitution rather than addition (36, 37), and it does not undergo polar addition of hydrogen chloride (12) or radical addition of 1-butanethiol (34). The observations that the basic hydrolysis of methyl 2,4,6-trimethylbenzoate proceeds by the usual attack of hydroxide ion at the carbonyl carbon (38), and that the acid-catalyzed hydrolysis of methyl α-(2,6-dimethoxyphenyl)vinyl ether proceeds by the normal mechanism involving nucleophilic attack of water at the benzylic carbon of the oxocarbenium ion intermediate (39), show that nucleophilic attack at the benzylic carbon of species of general structure **5** is not prohibited. However, in both of these cases, the ultimate product is itself of general structure **5** rather than the more sterically congested **6**. Our results suggest that the apparent inaccessibility of species of general structure **6** results primarily from their much smaller thermodynamic stability relative to **5**, so that **6** can be formed only when the reaction conditions do not permit for its rapid conversion to the more stable and sterically less congested **5**.

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